REMARKS

CLAIM REJECTION UNDER 35 U.S.C. § 102(b) BY WILTON ET AL.

Claims 1-5, 9, 12-14, and 26 stand rejected under 35 U.S.C. § 102(b) as anticipated by Wilton et al. This rejection is traversed.

As recited in claim 1, the claimed invention relates to a dual purpose primer for amplifying a target nucleotide sequence in a target molecule…wherein the primer comprises: (a) a primer sequence complementary to a segment of the target nucleotide sequence other than the secondary structure forming region and (b) a blocking sequence substantially complementary to a segment of the secondary structure forming region to prevent formation of the unwanted secondary structure.

In the Office Action under reply, the Examiner acknowledges that clause (a) of claim 1 recites a structural limitation. The basis of the Examiner's rejection of claim 1 lies in the Examiner's mistaken assertion that clause (b) recites a functional limitation of the claimed primers. While the recitation that the blocking sequence "prevent(s) formation of the unwanted secondary structure" is arguably a functional limitation, the recitation that the primer comprises "a blocking sequence substantially complementary to a segment of the secondary structure forming region" is unarguably a *structural* feature of the claimed primer.

The structural nature of the blocking sequence is disclosed throughout the specification. Directing the Examiner's attention to the figures, Figure 5 depicts a schematic of the dual purpose primer of the present invention. In Figure 5, the blocking sequence, shown by reference letter "B," is clearly shown as a *structural* segment of the primer. In paragraph 0019, the primer of Figure 5 is described as including a blocker sequence (B) and a primer sequence (P) wherein the P is complementary to one terminus of the target molecule that contains the SNP site (X) and B is substantially complementary to a sequence (B′) immediately adjacent to X; B′ being the segment of the target molecular responsible for generating an intramolecular secondary structure that in the absence of the dual purpose primer would conceal the SNP site from a complementary sequence (thereby preventing hybridization and detection). After amplification of the target molecular sequence and reannealing, B hybridizes with B′ thereby blocking formation of the unwanted secondary structure.

Figure 4 is a graph that shows how the blocking sequence enhances detection of exon 1 of the cytochrome P450 CYP2D2 gene (*see also*, paragraph 0018). Figure 6 is a gel, which shows that the dual purpose primers of the present invention with blocker sequence inserts of 8, 10, and 12 nucleotides all generate a major band of expected size (*see also*, paragraph 0020). In Figure 7, the blocking sequence (shown in orange) is again clearly shown as a *structural* segment of the primer. In Figure 8, the graph shows how the blocking sequence of the claimed primer enhances the net signal in SNP assays over the

signal obtained with a primer lacking the blocking sequence (*see also*, paragraph 0022). Lastly, Figure 10 shows how the blocking sequence of the primer physically hybridizes to the section of the target nucleotide sequence to disrupt the unwanted secondary structure formation.

As explained in response filed on November 8, 2006, Wilton et al. teach snapback primers that are designed to produce a PCR product that *retains* its secondary or tertiary structure so that the size of the PCR product may be determined by gel electrophoresis. In contrast to Wilton et al., the blocking sequence of the claimed dual purpose primers is designed to *disrupt* secondary structure so that a site of interest within a secondary structure formation may be identified. The structural difference between the snapback primer of Wilton et al. and the dual-purpose primer of the present invention is best seen by comparing Figures 1 and 3 of Wilton et al. with Figure 10 of the instant application.

In Figure 1 of Wilton et al., the C to T mdx mutation was investigated using the following six primers: forward primer A (A(f)); reverse primer B (B(r)); forward primer (C(f)); reverse primer D (D(r)), reverse snapback primer B (SB-B(r)), and reverse snapback primer D (SB-D(r)). As explained on page 254 (col. 2) of Wilton et al., the snapback primers SB-B(r) and SB-D(r) were designed from primers B(r) and D(r) with the addition at the 5′ terminus of the primers of 11 bases complementary to the normal mouse dystrophin sequence around the location of the mdx mutation. PCR products generated from a forward primer (i.e., A(f) or C(f)) and either of the snapback primers have terminal sequences that when in single-stranded form reanneal or snapback to the area under investigation. In other words, the 3′ or 5′ terminus of a single stranded PCR product has the potential to reanneal, or snapback, to the region of the mdx mutation. Figure 3 of Wilton et al. shows how the snapback primer folds back upon itself to form a loop (i.e., a secondary structure). In Figure 3, the 3′ terminus of the PCR product carrying the 11 bases complementary to the sequence around the mdx mutation (highlighted in bold) anneal or snapback back to the normal dystrophin sequence (highlighted with underlining) at the 5′ terminus of the PCR product thereby causing the formation of a secondary structure with the mdx mutation being present *within* the secondary structure (*see* page 257, col. 2). As explained at page 253 (col. 1), 257 (cols. 1 & 2), and 258 (col. 1) of Wilton et al., the conformation change resulting from the use of the snapback primers allows for the identification of the target nucleotides through altered migration of the target through a polyacrylamide gel.

By contrast, in Figure 10 of the instant application, it is shown how the dual purpose primer of the present invention anneals to two segments of a target nucleotide; specifically, one segment having a sequence located within an unwanted secondary structure region and another segment adjacent to the SNP site. As shown in Figure 10, the dual-purpose primer is able to anneal to two sections of the target nucleotide, which would otherwise not be accessible to amplification.

The foregoing discussion highlights the differences between the snapback primers of Wilton et al. and the dual-purpose primes of the present invention. Briefly, the snapback primers of Wilton et al. are designed for anneal to a *single* segment of a target nucleic acid such that PCR strands produced with the snapback primers have self-complementarity and are able to "snapback" upon themselves to form a loop, i.e., a secondary or tertiary structure, with the target nucleic acid located *within* the loop By contrast, the dual-purpose primer of the present invention is designed to anneal to *two* separate sections of a target nucleic acid - a segment outside of a secondary structure forming region and a segment within a secondary structure forming region - the end result being that the primer disrupts the secondary structure of the target nucleic acid to *expose* the target nucleic acid. As explained above, the blocking sequence of the claimed dual-purpose primer is the structural feature of the dual-purpose primer, which allows for the dual purpose primer to be able to disrupt the secondary structure of the target nucleic acid.

Because the snapback primer of Wilton et al. does not include a blocking sequence that is substantially complementary to a segment of the secondary or tertiary sequence disclosed therein, it follows that Wilton et al. does *not* teach or suggest the dual purpose primer of the claimed invention. Because the claimed invention is not anticipated or rendered obvious by Wilton et al, applicants request withdrawal of this rejection.

CLAIM REJECTION - 35 U.S.C. § 102(b) BY BANNWARTH ET AL.

Claims 1, 2, and 4-7 stand rejected under 35 U.S.C. § 102(b) as anticipated by Bannwarth et al. This rejection is traversed.

As explained in the response filed on November 8, 2006, Bannwarth et al. teach a self-complementary oligonucleotide that backfolds upon itself in order to form a double-stranded section; the oligonucleotide formed in Bannwarth et al. is similar to the PCR product produced in Wilton et al. At col. 2, ll. 17-34, of Bannwarth et al., the structure of the oligonucleotide is described; specifically, the oligonucleotide consists of a sequence substantially complementary to a segment of a target nucleic acid (Pp); a linking sequence (L), which serves to facilitate the backfolding; a sequence substantially complementary to Pp (Pc); and an energy source (X), which is used for detecting the oligonucleotide via energy transfer when the oligonucleotide is put in contact with a detection oligonucleotide. Figure 1 of Bannwarth et al. shows the configuration of the oligonucleotide when the Pp and Pc complementary strands anneal to form the double-stranded self-complementary oligonucleotide disclosed therein.

Contrary to the Examiner's assertion, Bannwarth et al. does *not* teach or suggest a blocking sequence as recited in claim 1. As explained above, Bannwarth et al. only discloses an oligonucleotide

with a sequence substantially complementary to a segment of the target nucleic acid and like Wilton et al., a self-complementary segment *within the same oligonucleotide*.

Because the oligonucleotide of Bannwarth et al. does not include a blocking sequence that is substantially complementary to a segment of a secondary structure, it follows that Bannwarth et al. does *not* teach or suggest the dual purpose primer of the claimed invention. Because the claimed invention is not anticipated or rendered obvious by Bannwarth et al., applicants request withdrawal of this rejection.

CLAIM REJECTION - 35 U.S.C. § 102(b) BY LAIBINIS ET AL.

Claims 1 and 5-8 stand rejected as anticipated under 35 U.S.C. § 102(b) by Laibinis et al. This rejection is traversed.

As explained in the response filed on November 8, 2006, Laibinis et al. teach a method for covalently linking a nucleic acid molecule having a target moiety to a support-bound oligonucleotide (i.e., a capture probe). The nucleic acid molecule is hybridized to the capture probe via complementary sequence, i.e., a pairing sequence on the nucleic acid molecule, which is covalently bound to a complementary sequence on the capture probe (para. 0010).

Contrary to the Examiner's assertion, Laibinis et al. does *not* teach or suggest a blocking sequence as recited in claim 1. As explained above, all that Laibinis et al. teach is the covalent bonding of a capture probe to a nucleic acid probe via complementary sequences. As noted in the prior response, the only mention in Laibinis et al. with respect to secondary or tertiary structure is at paragraph 0032 where it is stated that the target moiety may include secondary or tertiary structure. Laibinis et al.; however, does *not* suggest that the structures may be problematic and does *not* contemplate any reason or way to disrupt the secondary structure.

Because the oligonucleotide of Laibinis et al. does not include a blocking sequence that is substantially complementary to a segment of a secondary structure, it follows that Laibinis et al. does *not* teach or suggest the dual purpose primer of the claimed invention. Because the claimed invention is not anticipated or rendered obvious by Laibinis et al., applicants request withdrawal of this rejection.

CLAIM REJECTION - 35 U.S.C. § 103(a) OVER WILTON ET AL. IN VIEW OF STRATAGENE

Claims 27-30 stand rejected under 35 U.S.C. § 103(a) as obvious over Wilton et al. in view of the Stratagene Catalog. This rejection is traversed.

Claims 27-30 are kit claims that depend from claim 1. The primary reference, Wilton et al., is discussed above. The Examiner cites the Stratagene Catalog for the motivation to combine the reagents of claim 1 into a kit. Because the teachings of the Wilton et al. reference do not lead the ordinary artisan

to the claimed invention, the teachings of a kit from the Stratagene Catalog will not serve to render obvious the invention as recited in claims 27-30.

Because the Examiner's hypothetical combination of Wilton et al. in view of the Stratagene Catalog does not render the claimed invention obvious, applicants request withdrawal of this rejection.

CLAIM REJECTION - 35 U.S.C. § 103(a) OVER BANNWARTH ET AL. IN VIEW OF STRATAGENE

Claim 28 stands rejected under 35 U.S.C. § 103(a) as obvious over Bannwarth et al. in view of the Stratagene Catalog. This rejection is traversed.

Claim 28 is a kit claim that ultimately depends from claim 1. The primary reference, Bannwarth et al., is discussed above. The Examiner cites the Stratagene Catalog for the motivation to combine the reagents of claim 1 into a kit. Because the teachings of the Bannwarth et al. reference do not lead the ordinary artisan to the claimed invention, the teachings of a kit from the Stratagene Catalog will not serve to render obvious the invention as recited in claim 28.

Because the Examiner's hypothetical combination of Bannwarth et al. in view of the Stratagene Catalog does not render the claimed invention obvious, applicants request withdrawal of this rejection.

CLAIM REJECTION - 35 U.S.C. § 103(a) OVER BEATTIE ET AL. IN VIEW OF STRATAGENE

Claims 28-34 stands rejected under 35 U.S.C. § 103(a) as obvious over Beattie et al. in view of the Stratagene Catalog. This rejection is traversed.

Claims 28 to 31 are kit claims that depend from claim 1. The primary reference, Beattie et al., is discussed above. The Examiner cites the Stratagene Catalog for the motivation to combine the reagents of claim 1 into a kit. Because the teachings of the Beattie et al. reference do not lead the ordinary artisan to the claimed invention, the teachings of a kit from the Stratagene Catalog will not serve to render obvious the invention as recited in claims 28-31.

Claims 32-34 are directed to a hybridization probe that has the same elements as claim 1; accordingly the discussion of Beattie et al. set forth for claim 1 applies with equal force to claims 32-34.

Because the Examiner's hypothetical combination of Beattie et al. in view of the Stratagene Catalog does not render the claimed invention obvious, applicants request withdrawal of this rejection.

CLAIM REJECTION - 35 U.S.C. § 103(a) OVER WILTON ET AL. IN VIEW OF FISHER

Claims 10, 11, 15, and 16 stand rejected under 35 U.S.C. § 103(a) as obvious over Wilton et al. in view of Fisher. This rejection is traversed.

Claims 10, 11, 15, and 15 depend from claim 1. The primary reference, Wilton et al., is discussed above. The Examiner cites Fisher for the teachings of the non-natural bases iso-cytosine and iso-guanine. Because Wilton et al. do not teach or suggest the invention as recited in claim 1, the additional teaching of Fisher will not serve to render obvious the invention as recited in dependent claims 10, 11, 15 and 16.

Because the Examiner's hypothetical combination of Wilton et al. in view of Fisher does not render the claimed invention obvious, applicants request withdrawal of this rejection.

CONCLUSION

With this paper, each of the Examiner's rejections have been fully addressed and overcome. Because there will be no outstanding issues for this matter upon entry of this paper, applicants respectfully request withdrawal of all claim rejections and passage of this application to issue.

Lastly, applicants take this opportunity to remind the Examiner that the subject application has had a Rule 1.48 Petition pending since November 2006. Applicants respectfully request prompt consideration of the pending Petition.

Any questions regarding this paper or the application in general may be addressed to the undersigned attorney at 650-320-7662 or karen@canaanlaw.com.

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